II. REMARKS

Formal Matters

Upon entry of the amendments shown above, claims 66 and 68-83 are pending.

Claims 31, 35-38, 40-47, 51, 52, 59, 60, 62, 64, and 67 are cancelled without prejudice or disclaimer. Applicants reserve the right to file one or more continuing applications on the canceled subject matter.

Claims 66, 71, and 82 have been amended. Claims 66, 71, and 82 have been amended to delete the recitation of "inhibitor of ErbB1 activation" and to recite "cetuximab." Support for the amendment can be found throughout the specification, for example, at p. 26, paragraph [0081]. Thus, the amendments are fully supported by the specification and do not add new matter.

Rejection Under 35 U.S.C. §112, First Paragraph

Claims 31, 35-38, 41-47, 51, 52, 59, 60, 62, and 66-83 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement.

First, the Office alleges that the specification does not provide enablement for predicting the likelihood that a human colon cancer patient will exhibit a clinically beneficial patient response to treatment with erlotinib or gefitinib. Office Action at p. 7. The Office further alleges that the disclosure of a single monoclonal antibody (cetuximab) in the specification and data based on two monoclonal antibodies (cetuximab and EMD 27000) is not representative of the class of monoclonal antibodies that bind to ErbB1 and inhibit activation of ErbB1. Office Action at p. 11.

Second, the Office alleges that the graph previously submitted with Dr. Steve Shak's declaration shows only 21 circles and that 2 patients are unaccounted for. Office Action at p. 7. Moreover, the Office alleges that according to the graph, the 3 partial responders had LAMC2 values ranging between

approximately 3.1-5.25, whereas the 18 non-responders had LAMC2 values ranging between approximately 3.2-7.5. *Id.* The Office noted substantial overlap between the two groups, and that 10 of the 18 non-responders had LAMC2 values that fell within the 3.1-5.25 range. Office Action at p. 8. Based on this information, the Office alleges that one of skill in the art could not accurately predict the likelihood that a human colon cancer patient will exhibit a clinically beneficial response to treatment with either of these two drugs since 10 of the non-responders would have been predicted to respond based on their LAMC2 levels. *Id.*

Applicants respectfully traverse the rejection.

The test of enablement is whether one reasonably skilled in the art could make and use the invention from the disclosures in the application coupled with information known in the art without undue experimentation. MPEP §2164.01. The Office has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. MPEP § 2164.04. This can be done by making specific findings of fact, ***supported by the evidence***, and then drawing conclusions based on these findings of fact. *Id.* References should be supplied if possible to support a *prima facie* case of lack of enablement. *Id.* Specific technical reasons are always required. *Id.* If the Office has weighed all the evidence and established a reasonable basis to question the enablement for the claimed invention, the burden falls on applicant to present persuasive arguments, supported by suitable proofs where necessary, that one skilled in the art would be able to make and use the claimed invention using the application as a guide. MPEP § 2164.05. The evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art. *Id.* (emphasis original).

Without acquiescing to the rejection, and solely in an effort to expedite prosecution, the instant claims have been amended to recite a "method for predicting the likelihood that a human colon cancer patient will exhibit a clinically beneficial patient response to treatment with ***cetuximab*** . . . ."

Furthermore, Applicants enclose a second declaration by Dr. Steve Shak in which he submits a second graph (Exhibit 1) based on the same data set as the previously submitted graph, but individually shows the LAMC2 level for each patient. As can be seen in Exhibit 1, the LAMC2 expression levels in some patients appear identical or nearly identical to each other and therefore, the previously submitted graph may have appeared to show less than 23 circles.

The Office appears to question the data and asserts that one of skill in the art could not predict the likelihood that a human colon cancer patient will exhibit a clinically beneficial response to treatment because of some overlap in LAMC2 expression level between partial responders and non-responders. *See* Office Action at p. 7-8. However, the Office makes this assertion without any evidence and therefore fails to establish a *prima facie* case of nonenablement of the claims. Indeed, contrary to the Office's assertion, there is sufficient evidence that one skilled in the art may still predict the likelihood of cancer recurrence even though the raw data shows some overlap in gene expression levels between partial responders and non-responders overlap, if there is a statistically significant difference between the groups.

For example, Maitra et al. measured human telomerase (hTR) mRNA levels in samples obtained from 24 neuroblastoma (NB) patients and grouped the patients into those who exhibited "favorable" or "adverse" clinical outcome. *See* Maitra et al., "The RNA Component of Telomerase as a Marker of Biologic Potential and Clinical Outcome in Childhood Neurobastic Tumors," *Cancer* 85:741-749 (1999) at Figure 6. As shown in Figure 6, 16 patients showed favorable outcome, while 8 patients showed adverse outcome. Notably, hTR levels of 6 out of the 8 patients with adverse outcome overlapped with those patients that showed favorable outcome. If the Office's analysis is applied, one skilled in the art would not be able to predict outcome because of the overlap in hTR levels between the two groups. To the contrary, Maitra et al. concluded that "our data indicate that hTR may be able to predict the biologic

potential (and hence clinical outcome) in NBs." Maitra et al. at p. 748, col. 1, first paragraph. In its discussion of the data in Figure 6, Maitra et al. stated that:

> Figure 6 illustrates the hTR expression in 24 NBs as a correlate of clinical outcome . . . The 8 tumor samples from 7 patients with an adverse outcome (see above) had a mean hTR score of 3.1, which was significantly different from the mean hTR score of 1.3 in the 16 tumor samples associated with a favorable outcome ($P<0.001$, Wilcoxon's rank sum test). **Thus, our data indicate that hTR may be able to predict the biologic potential (and hence clinical outcome) in NBs**.

Maitra et al. at paragraph bridging p. 747-748 (emphasis added).

Similarly, Ball et al. measured HuD mRNA levels in 36 neuroblastoma (NB) tumor samples and grouped the samples into those that exhibited clinically favorable tumor stages (stages A, B, and DS) and those that exhibited clinically unfavorable stages (stages C and D). *See* Ball et al., "Neuron-Specific *Hel-N1* and *HuD* as Novel Molecular Markers of Neuroblastoma: A Correlation of *HuD* Messenger RNA Levels with Favorable Prognostic Features," *Clin. Cancer Res.* 3:1859-1865 (1997) at Figure 4. As shown in Figure 4, the HuD mRNA levels from most of the samples in clinically unfavorable stages overlap with those in clinically favorable stages. Nonetheless, Ball et al. found that the "mean level of *HuD* in favorable stages was significantly higher (0.98 ± 0.19) than unfavorable stages (0.47 ± 0.08, $P < 0.03$)." Ball et al. at p. 1862, col. 2. Based on this data, Ball et al. concluded that "high *HuD* mRNA levels may predict a clinically favorable outcome." Ball et al. at Abstract.

Like Maitra et al. and Ball et al., and as acknowledged by the Office, the instant specification at Table 3 shows that LAMC2 levels significantly correlated with a negative response (p value of 0.0357), wherein "negative" indicates that greater expression of the gene decreased the likelihood of response to treatment. Therefore, one skilled in the art may still predict the likelihood of response even though there was overlap in LAMC2 gene expression levels between the partial responder and non-responder patient groups.

Accordingly, Applicants believe that claims 31, 35-38, 41-47, 51, 52, 59, 60, 62, and 66-83 are fully enabled under 35 U.S.C. §112, first paragraph. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number GHDX-005.

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS LLP

Date: May 25, 2010

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